Herpesviruses in Fish

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Introduction

Herpesviruses cause diseases in a wide variety of animals including humans, monkeys, birds, cattle, horses, seals, dogs, rodents, snakes, turtles, frogs, oysters, and fish. The herpesviruses that infect fish produce several important diseases and some fish herpesviruses are regulated by both state and international law. In order to avoid serious losses, damage to the producer's reputation, and loss of access to markets, fish growers need to know about herpesvirus biology and about the important fish herpesviruses and.

The biology of herpesviruses is unusual. Herpesviruses are able to exist for many years in a resting stage in apparently-healthy carrier animals. During this stage (called "latency"), the genetic code of the virus hides within cells of the animal but no actual virus is produced. At a later time, the genetic code of the virus is reactivated and new virus is made. The newly made virus may cause disease in the infected animal, or the animal may continue to appear healthy but still shed virus that can infect and produce disease in other animals. An excellent example of this process is provided by "Chicken Pox" a very common human herpesvirus disease.

The Chicken Pox virus is so widespread in humans that almost all humans are infected by the time they are teenagers. When children are infected, they develop chicken pox disease and usually recover in a week or so. During the time they are sick, they shed virus that can infect other children. Once they have recovered, the infective virus is gone, but the genetic code for the virus continues to lurk in nerve cells. The virus may remain in this stage for the rest of the person's life, but in some individuals the combination of old age and stress makes conditions right for the virus to come out of hiding and cause a disease called "shingles". Adults experiencing an outbreak of shingles disease can spread the virus and cause chicken pox disease in children. In summary, almost all humans are infected by the chicken pox virus, survivors carry the genetic code of the virus forever, and at a later time when the immune system of those survivors is not fully functional the virus can come out of hiding and spread to new people.

Fish herpesviruses appear to behave very much like the human chicken pox herpesvirus. Fish that survive fish herpesvirus infections appear healthy and normal, but are likely to carry the genetic code of the herpesvirus. Those carrier fish may, under some stressful condition, release new virus into the water and infect fish that have not previously been exposed. Those newly infected fish may develop a disease, spread virus to other fish, and they become carriers that may also infect other fish at a later time. It is these healthy looking carrier fish that make it very difficult to control herpesviruses in fish.

In the sections below, we will look more closely at the fish herpesviruses of potential importance in the Southeastern US. There are many herpesviruses but the emphasis here is on those affecting commonly-cultured species of cyprinids and catfish.

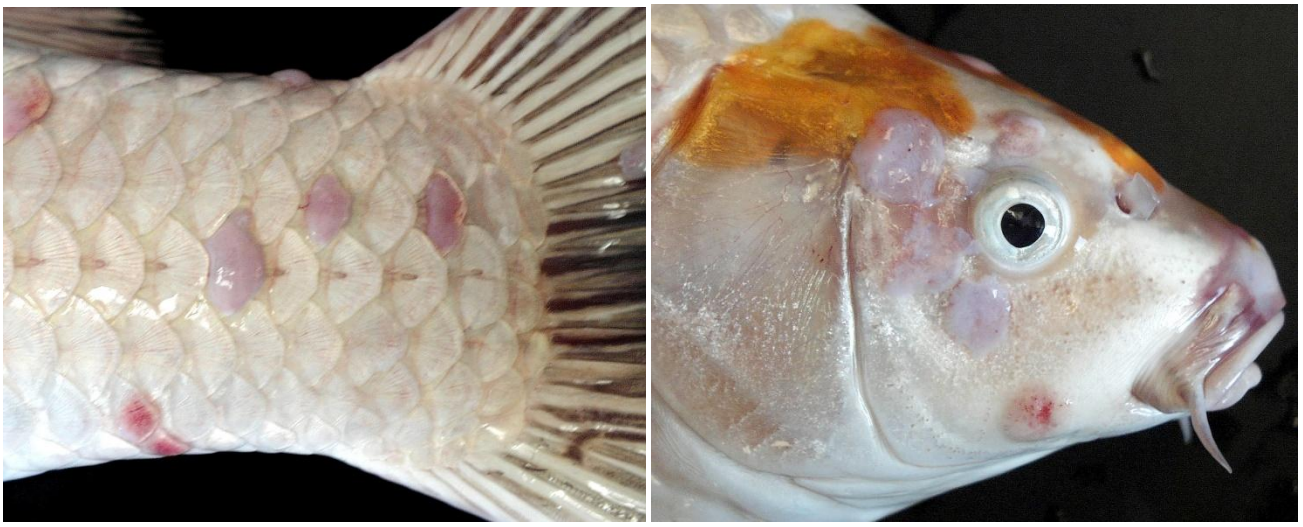
Carp, Koi, and Goldfish Herpesviruses

There are 3 herpesviruses that infect goldfish or koi. These viruses may have several names including common names and a scientific name.

Common name	Scientific name
Carp pox, Fish pox	*Cyprinid herpesvirus-1* (CyHV-1*)*
Herpesviral hematopoietic necrosis virus (HVHN) also known as Goldfish herpesvirus (GHV)	*Cyrpinid herpesvirus-2* (CyHV-2)
Koi herpesvirus (KHV)	*Cyprinid herpesvirus- 3* (CyHV-3)

Carp Pox: Of the koi and goldfish herpesviruses, carp pox is most like chicken pox in humans. The virus is globally distributed in koi and common carp. When the immune systems of infected fish are slowed by cold temperatures the virus sometimes produces a skin disease, but it is rare for fish to die. In almost all cases, warmer water temperatures help the fish to better respond to the infection and the skin heals. It is likely that these survivors are the source of the virus that infects the next generation.

The skin disease caused by the carp pox virus is quite easy to recognize. Diseased fish have soft, pink, translucent, wart-like growths on their skin. The growths are so fragile that they can usually be removed by gently rubbing a finger over the growth. This is not a good treatment for carp pox because the growth is likely to come back, and because the rubbing damages the skin making a secondary bacterial infection likely. However, verifying that the growths are soft and fragile does help to distinguish carp pox from some similar looking tumors and parasite infections. The best way to manage carp pox disease is to just wait for spring, or to slowly warm the fish to temperatures in the mid 70's to the mid 80's °F. It is very rare for fish to die from carp pox disease, but large growths do sometimes leave scars on valuable show fish. Therefore, it may be important to warm show fish that have carp pox disease when the growths are still in their early stages.



Caption: Typical carp pox growths on the skin of a koi.

Goldfish herpesvirus: The goldfish herpesvirus (GHV, also know as herpesviral hematopoietic necrosis virus or HVHN)was first reported back in 1995, but its importance was not understood until a new test was developed in 2006. We now know that the virus is global in distribution and that it can kill goldfish on farms, at small breeders, and even in back-yard pools and aquariums. Most goldfish populations carry the virus but, like carp pox, disease outbreaks are sporadic and are triggered by stress and water temperature. The disease is most common when water temperatures are in the 70's °F. It usually occurs in the spring and fall either when water temperatures first enter the 70's °F, or when fish from in ponds with warmer water are harvested and moved to holding facilities with cooler water.

The disease caused by GHV can take on several different appearances. The most common sign of the disease is anemia. The virus attacks the tissues (head kidney) that form new blood cells. Diseased fish therefore have low numbers of red blood cells, so their gills are pale. Another common sign of anemia in goldfish is a pale looking head. This paleness occurs because the fish's brain (somewhat visible through the goldfish's thin skull) is white instead of the usual pink. In other cases of GHV disease, there are small patches of dead gill tissue and the skin may lose the mucus and surface layers making it feel rough instead of smooth and slick.

The disease can be prevented if combinations of stress and temperatures in the 70's °F can be avoided. It can be treated by elevating temperatures into the low to mid 80's °F. At these higher temperatures, the fish's immune system is able to successfully defeat the disease. Of course, these surviving fish are GHV carriers.

Caption: A goldfish with normal red gills (above) and a goldfish with anemia and pale gills typical of GHV disease (below)

Koi Herpesviris: The other important cyprinid fish herpesvirus is koi herpesvirus (KHV). The KHV first appeared in the 1980's. After initial outbreaks in the US and Europe, it rapidly spread throughout the world to wherever koi and common carp are produced (with the possible exception of Australia). When it is first introduced into new fish populations, it may kill 70-95% of the fish. Its spread has had a devastating effect on koi producers and hobbyists and it has seriously reduced global production of farmed common carp, one of the world's most important protein resources. Today, the virus continues to cause sporadic disease outbreaks in farmed and wild common carp and koi populations.

Efforts to deal with KHV disease are very different from measures taken to prevent losses from carp pox and GHV. With carp pox and GHV, producers assume that the virus is present but make management changes to reduce disease losses. With KHV, producers, dealers, and hobbyists all work hard to prevent the introduction of KHV and infected populations are often destroyed to prevent the further transmission of the disease by survivors that carry KHV. Because the KHV is avoided instead of managed, biosecurity and sensitive tests for carrier fish are tremendously important. These issues will be discussed in later sections of this fact sheet.

The disease produced by KHV almost always includes patches of dead gill tissue. These patches are often white, but they may be yellow or brown if debris or bacteria stick to the damaged gill. In the early stages, the dead patches of gill may be surrounded by more normal-looking gill tissue. It is also fairly common for the skin to lose the mucus and surface layers so that it feels rough instead of smooth and slick. Care must be taken in the diagnosis because several common bacterial infections, including columnaris, can mimic KHV disease. Fish with KHV disease swim lethargically and congregate around aerators where it is easier for them to take up oxygen through their damaged gills. The disease usually occurs when infected fish are first held at water temperatures in the 70's °F. If temperatures are elevated into the 80's, many fish will recover and be immune to further KHV disease, however, these survivors are carriers and they are a threat to other koi at koi shows or when sold or moved to new collections where KHV disease has not previously occurred. Survivors of KHV

outbreaks should never be sold or taken to koi shows. Most producers and breeders elect to destroy infected koi and carp populations to prevent spread of the disease.

Caption: Koi with KHV infection. The fish on the left is at the early stages and has sharp-edged white patches of gill tissue. The fish on the right has a more advanced case of KHV with widespread destruction of gill tissue.

Caption: This fish does NOT have KHV. The white patches of gill tissue are the result of a columnaris bacterial infection. Also noticeable on this fish is a “notched nose”. Some koi owners consider a “notched nose” to be a sign of KHV disease, but it is also clearly noticeable on this fish that has only a bacterial infection.

Catfish Herpesviruses

There are two known herpesviruses of catfish. These are the Channel Catfish Virus (CCV) and a herpesvirus of black bullheads. The scientific names for these viruses are *Ictalurid herpesvirus-1* (IcHV-1) and *Ictalurid herpesvirus-2* (IcHV-2).

The CCV is widespread in North America. It has been shown to be present in almost all commercial populations of channel catfish. Given that channel catfish are also very common species in state hatchery and stocking programs, it is also very likely that CCV is widespread in wild catfish populations. As with carp pox and the GHV, catfish producers assume that the virus is present and manage their facilities to reduce the probability that the disease will develop.

The CCV produces disease in young catfish during their first summer in production ponds. It typically occurs in the Southeastern USA during the summer months when water temperatures are above 90 °F. Outbreaks of disease in fish older than six months, or at cooler temperatures, are extremely rare, but there have been reports of CCV disease occurring in fry still held in hatchery tanks at temperatures in the 80's. The CCV disease is not a major problem in the catfish industry, but it does cause serious losses in fingerling ponds when the disease does occur. The CCV disease has never been reported in wild fish populations or in the northern half of the US where water temperatures rarely reach the 90 °F threshold associated with CCV disease in the Southeast. The primary method for the management of CCV is to avoid handling or other stresses during the summer months when young fish are experiencing temperatures above 90F. Disease caused by CCV could probably be treated by cooling fish to temperatures well below the 90 °F threshold where the disease occurs, but this is rarely practical in large commercial production ponds during the summer months. Farmers sometime turn on supplies of cool well water in the hope that the fish will take refuge in the cooler waters near the inlet pipe.

The primary sign of CCV disease in channel catfish fingerlings is a bloated, fluid filled abdomen. The CCV disease often occurs with infections of columnaris bacteria. The CCV disease can easily be confused with outbreaks of ESC disease that may produce similar bloating under some conditions.

Caption: These very famous pictures of CCV disease are from the collection of Dr. John Plumb. The fish on the left has a swollen abdomen and pop-eye typical of CCV. The fish on the right have CCV, but also a co-infection by columnaris bacteria. The swollen abdomen is from CCV while the eroded fins and tails are due to columnaris disease.

The other important herpesvirus of catfish is IcHV-2. The IcHV-2 was first reported in farmed black bullheads in Italy back in the early 1990's. Within a few years, the virus spread rapidly and decreased the

production of farmed black bullhead in Italy by more than 90%. The IcHV-2 has never been reported in North America, but if introduced here it clearly has the potential to cause serious harm to wild and farmed populations of bullhead catfish. More troubling is that it has been shown experimentally that channel catfish are very susceptible to IcHV-2 and that in parallel exposure experiments the IcHV-2 virus kills more fish than does CCV. The IcHV-2 disease also occurs at cooler temperatures than CCV disease (the 70's rather than the 90's °F), so it would be likely to produce disease over a broader geographic region. It is extremely important that IcHV-2 is not introduced into North America.

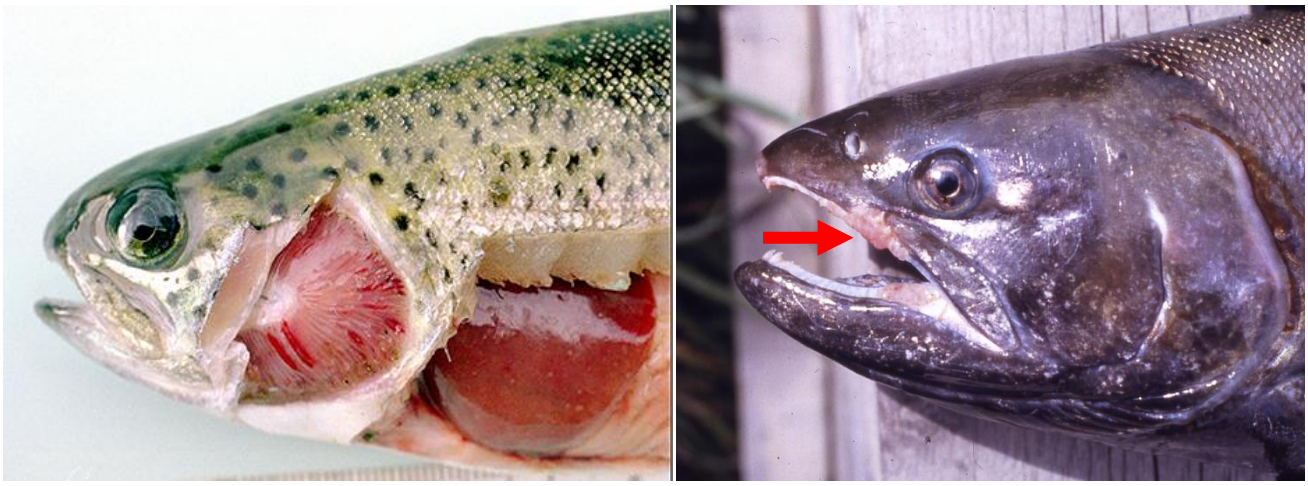
Sturgeon Herpesviruses

There are several herpesviruses found in sturgeon. Two of the most important were called *White Sturgeon Herpesvirus 1* (WSHV-1) and *White Sturgeon Herpesvirus 2* (WSHV-2), but they are now formally recognized as *Acipenserid herpesvirus* 1 and *Acipenserid herpesvirus 2* (AciHV-1 and AciHV-2)). In young sturgeon (less than 6 months of age) both herpesviruses have been associated with mortality of up to 50%. The viruses tend to target fish that are feeding well and growing rapidly. In these young fish it is unusual for these viruses to produce lesions visible to the naked eye, but microscopy reveals severe damage to skin cells. The AciHV-2 also produces a disease in older fish where white blisters and ulcers are seen on the skin. Mortality from this form of the disease rarely exceeds 10%. The AicHV-2 has also been shown experimentally to kill juvenile shovelnose and pallid sturgeon. Both herpesviruses are present in wild sturgeon populations in the western USA and are of great importance in sturgeon aquaculture, especially when wild broodstock are used.

Caption: The tail of a white sturgeon experimentally infected with AicHV-2. Note the soft translucent skin growths that resemble those of carp pox.

Trout and Salmon Herpesviruses

There are two well-known herpesviruseses of salmonids. They are named *Salmonid herpesvirus* 1 (SalHV-1) and *Salmonid herpesvirus* 2 (SalHV-2, common name *Oncorhynchus masou* virus or OMV). The SalHV-1 was initially isolated from rainbow trout in Washington State, but it is not an important cause of disease. The other trout and salmon herpesvirus, OMV, does cause an important disease in Pacific salmon and in rainbow trout. The disease is usually characterized by skin ulcers and red or white spots in internal organs. Survivors often develop tumors in their jaws. The disease most commonly occurs in 1-month-old alevins and at temperatures below 57 °F. The OMV is found only in Japan and has never been reported in North America. It is very important that we are all careful not to introduce this virus.



Caption: On the left is a rainbow trout with OMV disease. The pale gills and white spots on the liver are typical of OMV. On the right is a wild Masu salmon with a jaw tumor (arrow) caused by OMV. Pictures courtesy of Dr. Mamoru Yoshimizu of Hokkaido University, Japan.

Avoiding Herpesviruses

Some fish herpesviruses are so widespread that avoidance is essentially impossible. These would include carp pox (CyHV-1), the herpesvirus of goldfish (CyHV-2), and channel catfish virus (IcHV-1). For these viruses, management to prevent disease outbreaks is the correct approach (see "Managing Herpesviruses", the next section of this fact sheet). The other fish herpesviruses are still limited in distribution. For these, the best approach is to take measures to ensure that they are not brought onto the farm.

Herpesviruses can enter a farm through infected fish, contaminated water supplies, contaminated equipment, and human and animal visitors. All of these routes should be addressed in a farm biosecurity plan as described in SRAC Fact Sheet ####. One of the most important parts of a biosecurity plan is ensuring that infected fish are not brought onto the farm. Unfortunately, the ability of the herpesviruses to persist in healthy-looking survivors can make detection of infected fish very difficult.

Fish that survive herpesviruses carry the genetic code for the virus, but most of the time few if any actual infectious virus is present. This means that tests to detect herpesviruses by cell culture (the standard practice with fish viruses) will almost always turn up a negative result even when the fish actually carry the virus. Cell cultures are useful to diagnose herpesvirus infections during those times when fish are sick with the disease, but are essentially useless for detecting carriers. Another approach is to test fish for the genetic code (DNA) of the virus. These tests go by the acronym "PCR" (the polymerase chain reaction). The PCR tests are very sensitive and specific and are a better tool for detecting carrier fish than is cell culture, but PCR may still fail to detect very low level carriers. The PCR tests are also not currently recognized to test fish for regulatory purposes but they are used to identify viruses grown in cell cultures.

The other way to test for herpesviruses is to look for evidence that the fish has been exposed to a herpesvirus. When fish are exposed to a herpesvirus and then begin to develop disease, their immune systems produce virus fighting molecules called antibodies. These antibodies persist in the fish's blood for months or years following the disease. With some herpesviruses, most notably KHV, it is possible to draw blood samples from fish and submit them to a few specialized labs that can detect the antibodies. If the antibodies are present, it means that the fish has been exposed to the herpesvirus and is likely a carrier. These tests are able to detect survivors for months or years after the disease outbreak.

The other big testing challenge with fish herpesviruses is with fish that have been exposed to the virus but have not yet developed the disease. These fish have too few viruses to be detected by any method and

have not yet produced antibodies. Thus, exposed fish that have not yet had the disease are a very great risk for disease transmission, but are undetectable by laboratory testing.

Keeping herpesvirus infected fish off of a farm takes more than testing. To the greatest extent possible, use farm-raised broodfish and do not bring new fish onto the farm unless absolutely necessary. If new broodfish must be brought onto the farm, they should be obtained from a source that has a program to prevent herpesvirus infection. Wild broodfish are the most risky. If new fish are brought onto the farm, quarantine them wity careful biosecurity (SRAC Fact Sheet ###) until they have experienced several weeks (at least 3) at the water temperature where the herpesvirus of concern is likely to cause disease. Test any sick fish by cell culture. After the quarantine, test the survivors by PCR or an antibody test (if available).

A common aquaculture biosecurity practice is to isolate new broodfish, disinfect their eggs with iodine, and to then move only the disinfected eggs onto the main farm. While this is always an excellent idea, it is important to be aware that this strategy may not offer full protection from herpesviruses. There is convincing evidence that egg disinfection often fails with herpesviruses. It is possible that fish herpesviruses may be transmitted within eggs instead of on the egg surface. Virus inside the egg is protected from the iodine by the egg shell.

In summary, avoiding herpesviruses is achieved by the following measures.

- Use on-farm broodstock and avoid new fish introductions if possible
- If new fish are introduced, get them from reliable sources with good histories and not from the wild.
- Quarantine new fish and then test for the virus.
- Don't rely on egg disinfection to prevent herpesvirus introductions.

Treating Herpesvirus Infections

If fish are infected by herpesviruses, there are very few treatment options. **There are no treatments that can be used to clear the virus from carrier fish**. If fish are dying during an outbreak of disease, losses can be greatly reduced by manipulating water temperatures. Most herpesviruses produce disease only at certain temperatures. Moving sick fish out of those temperatures greatly reduces mortality and these survivors are generally resistant to future disease caused by the same virus, however, you must keep in mind that **all herpesvirus survivors are carriers with the potential to spread the virus to new places.** Temperature treatments are not appropriate unless there will be no opportunities for the survivors to spread virus to new fish populations. Outbreaks of KHV and the goldfish herpesvirus disease can be treated by elevating water temperatures into the mid 80's °F but any fish treated in this manner must be considered virus carriers with the potential to infect other fish. Signs of carp pox disease disappear at water temperatures over about 72 °F. Channel catfish virus losses are greatly diminished by reducing water temperatures into the 70's.

Vaccination

At the time this article was written, there are not any vaccines in the US for fish herpesviruses. There is a KHV vaccine available in some other countries. Vaccines are an attractive method to help avoid the introduction of KHV or to prevent disease outbreaks from widely distributed viruses like the goldfish herpesvirus and CCV. If effective, practical, and economically feasible vaccines do become available for fish herpesviruses in the US, they will be of great benefit, but there are two important things that should be kept in mind. The first is that vaccinated fish are likely to test positive by PCR and antibody tests. There may be no way to distinguish safe vaccinated fish from dangerous carriers. The other concern is that there is the potential that vaccinated fish, while protected from the disease, may still be able to serve as virus carriers.

Managing Herpesviruses

Avoidance is always best, but some herpesviruses like carp pox (CyHV-1), the herpesvirus of goldfish (CyHV-2), and channel catfish virus (IcHV-1) are so widespread that avoidance is nearly impossible. The best approach for these viruses is to manage your farm in a way that decreases the likelihood of a disease outbreak and that minimizes losses should an outbreak happen. In general, disease outbreaks are prevented by avoiding stress during the temperatures and seasons where the disease is likely to occur.

Carp pox: The virus is widespread so avoidance is almost impossible. The best management for carp pox is to make sure that koi and common carp have adequate nutrition, good water quality, and low parasite loads during the winter when temperatures are low. If it is possible, try to avoid very low temperatures in the winter and rapid temperature changes.

The goldfish herpesvirus (CyHV-2): The virus is widespread so avoidance is almost impossible. It appears that goldfish fry are often carrying the virus when they leave the hatchery. Disease occurs the first time that water temperatures drop into the lower 70's °F at the same time a stressful event occurs. The disease is often seen in young fish during periods of fluctuating fall temperatures. If fall temperatures drop rapidly through the 70s to colder temps, losses are minor, but if temperatures drop into the 70's and remain there for some time, significant losses may result. The best scenario is to have temperatures drop briefly into the 70's and then move back into the 80's for some time. When this temperature pattern occurs, fish begin to develop the disease, but the elevation in temperature slows the virus and gives the fish time to make a strong immune response. These fish may then be immune to the disease when the temperatures drop again later.

A very common trigger for goldfish herpes virus (CyHV-2) disease in the Southeast is mid-summer harvest and handling. If fish are stocked out and grown at high temperatures the carriers do not develop disease. However, when the farm harvests and moves fish to cooler holding facilities (especially if that move involves long-distance shipment at cool temperatures) outbreaks of the disease are likely to occur. These outbreaks can be prevented by gentle handling at the highest temperatures consistent with good survival. It has also proven to be very helpful if fish are held at warm temps (in the 80's °F) following summer shipments at cool temperatures.

Channel catfish virus (CCV): The virus is widespread so avoidance is almost impossible. Disease most often occurs when young of the year fish are stressed at water temperatures in the 90's. Thus, the dangerous time of year in the Southeast is July through August. Disease is usually triggered by harvest or poor water quality occurring during the hottest part of the summer. Reducing losses when disease outbreaks occur is possible if temperatures can be reduced, but this is very difficult in large earthen ponds. Running cool well water may help, but even large flows of well water have small effects on pond temperatures. Harvesting sick fish and moving them to cool water in a holding facility is generally not done because the harvesting stress is likely to make things worse. In managing CCV outbreaks, it is also important to consider that columnaris disease often co-occurs with CCV.

Summary

- There are many important herpesviruses of fish.
- Survivors of herpesvirus infections carry the virus and may infect other fish at a later time.
- Carriers are extremely hard to detect using laboratory tests.
- Some herpesviruses have limited distribution so the best protection is a good biosecurity program to prevent introduction (Oncorhynchus masou virus (SalHV-2), koi herpesvirus (CyHV-3), *Ictalurid herpesvirus*-2 (IcHV-2), sturgeon herpesviruses (AciHV-1 and AciHV-2)

- Other herpesviruses are widespread but losses can be prevented by careful management of stress during disease temperature windows (carp pox (CyHV-1), goldfish herpesvirus (CyHV-2), channel catfish herpesvirus (IcHV-1)
- When outbreaks of herpesvirus diseases occur, losses can be minimized through temperature manipulation, but **survivors of the outbreak will be carriers** of the virus
- There are no drug or chemical treatments useful for herpesvirus infections in fish.